## REMARKS

Claims 1-7, 9-20, 46-66, 80 and 83 are pending. The specification has been amended to reflect the claim of priority. A substitute declaration has been submitted herewith. Claims 9, 11, 14, 16, 47, 65, and 66 have been canceled, without prejudice. Claims 1, 4, 7, 10, 12, 13, 15, 17, 18, 20, 46, 48, 52, 55, 56, 58 and 64 have been amended. Support for the amendments can be found, for example, throughout the specifications as originally filed.

Claims 10, 12, 13, 15, 17, and 48 have been amended to be dependent on a pending claim. Support for the amendment to claim 46 can be found, for example, in claim 47. Support for the amendment to claim 1 can be found, for example, on page 8. Claims 7, 52, 55 and 58 have been amended to recite Markush language. No new matter has been added. After entry of the amendment, claims 1-7, 10, 12, 13, 15, 17-20, 46, 48-64, 80 and 83 will be pending.

Attached hereto is a marked-up version of the changes made to the specification and claims by the present amendment. The attached page is captioned "**Version with markings to show changes made**".

Claims 7 and 9-18 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Claim 7 has been amended to recite proper Markush format and claims 9-18 have been amended to depend from pending claim 1. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 1-7 and 9-10 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,591,840 to Narayanan et al. ("the Narayanan patent"). Applicants do not concur with the rejection. The Office Action suggests that "oligomers

associated with targeted carriers such as antibody or receptor fragments, ligand molecules, hormones, and enzymes . . . [and] liposomes or micelles for more efficient delivery into cells," as discussed in the Narayanan patent, anticipates the present claims that recite penetration enhancers (Office Action, p.1). However, the Office Action selectively quotes the specification at page 8, lines 4-15 in order to support the rejection. The entire relevant passage reads as follows:

> Penetration enhancers facilitate the transport of drug molecues, for example, oligonucleotides and other nucleic acids, across mucosal and other epithelial cell membranes. Penetration enhancers include, but are not limited to, members of molecular classes such as surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactant molecules.

(Specification, page 8, lines 6-12). The Narayanan patent does not disclose penetration enhancers as recited in the present claims. Accordingly, the discussion of conjugated oligomers does not anticipate the present claims, which are directed to delivery of an oligonucleotide with particular types of penetration enhancers. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 1-7, 19-20, 46-64, 80 and 83 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,111,094A1 to Bennett et al. (hereinafter "the Bennett patent"). In view of Applicants' claim of priority, the present application is entitled to an effective filing date of July 1, 1997.[1] The disclosure in the Bennett patent that serves as the

[1] As provided on page 37 of the present application, SEQ ID NO:1 (ISIS-2302) has the same base sequence as SEQ ID NO:55 (ISIS-15839). Although the specification as originally filed identifies ISIS-2302 and ISIS-15839 by the same SEQ ID NO, the amendment filed on June 12, 2000, sets forth the current identification as SEQ ID NOS: 1 and 55, respectively. Support for the claim of priority can be found throughout the specification of Application Serial No. 08/886,829 as originally filed, for example, in Table 1 on pages 46-47.

basis for the rejection is not disclosed in its immediate parent (U.S. Patent No. 5,843,738). Thus, the subject matter over which the present inventions stand rejected has an effective filing date of April 17, 1998, the date on which the Bennett patent was filed. Accordingly, the Bennett patent no longer constitutes a proper § 102(e) reference. Applicants therefore respectfully request withdrawal of the rejection.

Claims 46 and 65-66 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,120,803A to Wong et al. (hereinafter "the Wong patent"). In view of Applicants' claim of priority, the present application is entitled to an effective filing date of July 1, 1997. Accordingly, the Wong patent, which was filed on August 10, 1998, does not qualify as prior art under 35 U.S.C. § 102(e), and cannot provide the basis for a rejection. Applicants therefore respectfully request withdrawal of the rejection.

Claims 46, 52-53, 56-57 and 59-61 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,853,748-A to New et al. (hereinafter "the New patent"). Applicants respectfully request reconsideration and withdrawal of this rejection as the Office Action fails to establish anticipation.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631 (Fed. Cir. 1987); *MPEP* § 2131. The identical invention must be shown in as complete detail as is contained in the . . . claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); *MPEP* § 2131.

The Office Action rejects the claims based on the fact that the New patent discusses antisense oligonucleotides and their analogues. Although Applicants do not concur with the rejection, solely for purposes of advancing prosecution, the claims have been amended to recite a preferred embodiment, wherein the oligonucleotide comprises at least one modified covalent linkgage. As such, the New patent does not recite each element of the present claims and, therefore, does not anticipate. Applicants request reconsideration and withdrawal of the rejection.

Claims 1-7, 9-20 and 46-62 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,877,309-A to McKay et al. (hereinafter "the McKay patent"). In view of Applicants' claim of priority, the present application is entitled to an effective filing date of July 1, 1997. Accordingly, the McKay patent, which was filed on August 13, 1997, does not qualifies as prior art under 35 U.S.C. § 102(e), and cannot provide the basis for a rejection. Applicants therefore respectfully request withdrawal of the rejection.

Applicants respectfully submit that the claims presently before the Examiner patentably define the invention over the prior art and are otherwise in condition for ready allowance.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES

**In the Specification**

Please amend the first full paragraph on page 1 under the heading Cross Reference to Related Applications" (starting at line 5 and ending on line 8) as follows:

[This application is a continuation-in-part of U.S. patent application serial no. 09/082,624 filed on May 21, 1998, the disclosure of which is incorporated by reference herein in its entirety.]

This application is a continuation of application serial no., 09/108,673 filed July 1, 1998, which is a continuation-in-part of application serial no. 08/886,829 filed July 1, 1997 (abandoned).

**In the Claims**

Please cancel claims 9, 11, 14, 16, 47, 65, and 66, without prejudice, and amend claims 1, 4, 7, 10, 12, 13, 15, 17, 18, 20, 46, 48, 52, 55, 56, 58 and 64 as follows:

1. (Amended) A composition comprising at least one oligonucleotide in an emulsion and [a penetration enhancer] at least one penetration enhancer selected from the group consisting of surfactants, fatty acids, bile salts, chelating agents, non-chelating non-surfactant molecules, and combinations thereof.

4.(Amended) The composition of claim 1 wherein said oligonucleotide is [selected from the group consisting of] a ribozyme [,] or a peptide nucleic acid [, a molecular decoy, an external guide sequence and an aptamer].

7.(Amended) The composition of claim 6 wherein said microemulsion is selected from the group consisting of an oil-in-water microemulsion, a water-in-oil microemulsion, an oil-in-water-in-oil microemulsion and a water-in-oil-in-water microemulsion.

10. (Amended) The composition of claim [9] 1 wherein said fatty acid is selected from a group consisting of arachidonic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, a monoglyceride, a diglyceride and a pharmaceutically acceptable salt thereof.

13.(Amended) The composition of claim [8] 1 wherein said penetration enhancer is a combination of at least one fatty acid and at least one bile salt.

15. (Amended) The composition of claim [14] 1 wherein said chelating agent is selected from the group consisting of EDTA, citric acid, a salicyclate, an *N*-acyl derivative of collagen, laureth-9, an *N*-amino acyl derivative of a beta-diketone and a mixture thereof.

17. (Amended) The composition of claim [16] wherein said surfactant is selected from the group consisting of sodium lauryl sulfate, polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether, a perfluorchemical emulsion and a mixture thereof.

18.(Amended) The composition of claim [8] 1 wherein said [penetration enhancer] non-chelating non-surfactant is selected from the group consisting of unsaturated cyclic ureas, 1-alkyl-alkanones, 1-alkenylazacyclo-alakanones, steroidal anti-inflammatory agents and mixtures thereof.

20.(Amended) The composition of claim 19 wherein said carrier compound is selected from the group consisting of polyinosinic acid, dextran sulfate, polycytidic acid, [lipofectin, cationic glycerol derivatives, polylysine] and 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid.

46. (Amended) A composition comprising an oligonucleotide in oral dosage form, wherein said oligonucleotide comprises at least one modified covalent linkage.

48. (Amended) The composition of claim [47] 46 wherein said modified covalent linkage is selected from the group consisting of a phosphorothioate linkage, a phosphotriester linkage, a methyl phosphonate linkage, a methylene(methylimino) linkage, a morpholino linkage, an amide linkage, a polyamide linkage, a short chain alkyl intersugar linkage, a cycloalkyl intersugar linkage, a short chain heteroatomic intersugar linkage and a heterocyclic intersugar linkage.

52. (Amended) The composition of claim 46 wherein said oral dosage form is selected from the group consisting of tablets, and capsules [and gel capsules].

55. (Amended) The composition of claim 46 wherein said nucleic acid is a ribozyme [,] or a peptide nucleic acid [an external guide sequence, a molecular decoy or an aptamer].

56. (Amended) The composition of claim 46 further comprising an enteric material that substantially prevents dissolution of said tablets [,] or capsules [or gel capsules] in a mammalian stomach.

58. (Amended) The composition of claim 57 wherein said enteric coating is selected from the group consisting of acetate phthalate, propylene glycol, and sorbitan monoleate [cellulose acetate trimellitate, hydroxy propyl methyl cellulose phthalate or cellulose acetate phthalate].

64. (Amended) The composition of claim 63 wherein said excipient is [selected from the group consisting of] polyethyleneglycol [and precirol].